Preeclampsia Recurrence and Prevention

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Preeclampsia Recurrence and Prevention

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Women with a previous pregnancy complicated by preeclampsia have an increased risk for recurrence in subsequent pregnancies. For severe preeclamptic women in an initial pregnancy, recurrence rates for any type of preeclampsia are very high, approaching 50% in some studies. Significant maternal and fetal complications are more common in recurrent preeclampsia compared with an initial episode. For women who have experienced a pregnancy complicated by preeclampsia, a systematic evaluation for underlying risk factors may identify a specific pathway suitable for a specific intervention. Although some progress has been made in developing potential therapeutic options to prevent preeclampsia recurrence, there is a great need for better data to determine who will benefit most from any specific therapy.

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Preeclampsia complicates approximately 5% to 10% of nulliparous pregnancies[1] and is consistently among the top three causes of maternal death in both developed and developing countries.[2-4] Two-thirds of cases will be mild and the other third severe in degree.[1] Preeclampsia is considered a disease of nulliparous women, as it is twice as common in primigravidas as it is in women who have previously given birth.[5] It is well known that women with a previous pregnancy complicated by preeclampsia have an increased risk for recurrence in subsequent pregnancies. For severe preeclamptic women in an initial pregnancy, recurrence rates for any type of preeclampsia are very high, approaching 50% in some studies. Significant maternal and fetal complications are more common in recurrent preeclampsia compared with an initial episode. Thus, accurate and thorough counseling regarding recurrence risks and potential preventive measures will assist women and their caregivers to make important decisions pertaining to future childbearing.

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Preeclampsia Risk Factors

Many factors for preeclampsia have been described in the obstetrical literature, and the majority will persist in subsequent pregnancies (Table 1).[6] Preeclampsia tends to be a disease of first pregnancy in women with no other obvious risk factors; however, underlying medical conditions with vascular or renal implications (diabetes mellitus, chronic hypertension) and conditions with increased trophoblast mass (multifetal gestation or hydrops fetalis) substantially increase the risk. As preeclampsia is likely a syndrome of multiple etiologies and many underlying factors persist across pregnancies, a significant risk factor for future preeclampsia is a prior history of preeclampsia.

The Epidemiology of Preeclampsia Recurrence

A number of studies have examined the risk for preeclampsia recurrence in subsequent pregnancies, and all have indicated a significantly increased risk (Table 2). The highest risks for recurrence are found most consistently when the initial case was preterm, severe, or complicated by eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, or fetal growth restriction. However, good data are still relatively sparse because definitions for preeclampsia often vary from study to study.

Campbell and coworkers studied a population of pregnant women (n = 29,851) whose first recorded pregnancy occurred between the years 1967 and 1978 in Aberdeen, Scotland and had >2 subsequent pregnancies during that same

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Table 1 The Strength of the Association of Selected Risk Factors for Preeclampsia*

Risk Factor Associated with Preeclampisa	Reference	OR (95% CI)
Preeclampsia in a previous pregnancy	Hnat[18]	3.88 (2.98-5.05)
	Duckitt[48]	7.19 (5.85-8.83)
First pregnancy	Conde-Agudelo[49]	2.38 (2.28-2.49)
	Duckitt[48]	2.91 (1.28-6.61)
Multifetal gestation	Sibai[50]	2.62 (2.03-3.38)
	Conde-Agudelo[49]	2.10 (1.90-2.32)
	Duckitt[48]	2.93 (2.04-4.21)
Chronic hypertension	Conde-Agudelo[49]	1.99 (1.78-2.22)
Gestational diabetes	Conde-Agudelo[49]	1.93 (1.66-2.25)
Pregestational diabetes	Duckitt[48]	3.56 (2.54-4.99)
Vascular and connective tissue disease	Stamilio[51]	6.9 (1.1-42.3)
Nephropathy		
Urinary tract infection	Abi-Said[52]	4.23 (1.27-14.06)
Antiphospholipid antibody syndrome	Robertson[53]	2.73 (1.65-4.51)
	Duckitt[48]	9.72 (4.34-21.75)
Genetic factors (eg, thrombophilias)	Robertson[53]	
Factor V Leiden heterozygosity		2.19 (1.46-3.27)
Prothrombin heterozygosity		2.54 (1.52-4.23)
MTHFR homozygosity		1.37 (1.07-1.76)
Hyperhomocysteinemia		3.49 (1.21-10.11)
Obesity (BMI >35 kg/m^2)	Sibai[1]	3.38 (1.91-6.00)
Maternal age >35 years	Conde-Agudelo[49]	1.67 (1.58-1.77)
Family history of preeclampsia	Duckitt[48]	2.90 (1.70-4.93)
Fetal malformation	Conde-Agudelo[49]	1.26 (1.16-1.37)
Abnormal maternal serum markers (AFP, hCG, uE3, Inhibin A)	Dugoff[54]	
Inhibin A >2.0 MOM		2.39 (1.75-3.26)
2 abnormal markers		3.65 (2.79-4.78)
African-American race	Tucker[55]	1.2 (0.8-1.7)

Abbreviations: AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated estriol.
*Presented as odds ratio (OR) and 95% confidence intervals (CI).

time period (n = 6637).[7] Women were categorized as normotensive (68.0%), mildly preeclamptic (26.3%), proteinuric preeclamptic (5.6%), and eclamptic (0.2%). They found that the overall incidence of preeclampsia in a second pregnancy was less than that in a first pregnancy, but was dependent on the outcome of the first pregnancy. If the first pregnancy was complicated simply by proteinuric preeclampsia, the incidence in the second pregnancy was 7.5%, whereas those who were normotensive in the first pregnancy had a low rate of proteinuric preeclampsia in the second pregnancy

Table 2 Summary of Studies that Present the Risk for Recurrence of Preeclampsia

Author	Study Population	Rate of Recurrence
Campbell[7]	Preeclampsia (n = 279)	Preeclampsia 7.5%
Sibai[9]	Second trimester severe preeclampsia (n = 169)	Any preeclampsia 65% <28 weeks 21% 28-36 weeks 21% 37-40 weeks 24%
van Rijn[8]	Preeclampsia with delivery <34 weeks	Preeclampsia 25%
Sullivan [12]	HELLP (n = 161)	Preeclampsia 43% HELLP 27%
Sibai[11]	HELLP (n = 192)	Preeclampsia 19% HELLP 3%
Chames[13]	HELLP with delivery <28 weeks (n = 62)	Preeclampsia 55% HELLP 6%
Adelusi[14]	Eclampsia (n = 64)	Eclampsia 16%
Sibai[16]	Eclampsia (n = 366)	Preeclampsia 22% Eclampsia 2%
Trogstad[17]	Preeclampsia singleton (n = 19,960)	Preeclampsia 14.1%
	Preeclampsia twins (n = 325)	Preeclampsia 6.8%

of 0.7%. However, women who had proteinuric preeclampsia in conjunction with a low-birth-weight (<2500 g) infant in their first pregnancy had double the incidence of proteinuric preeclampsia in their second pregnancy (11.9% versus 6.6%), compared with similar women with a normal infant birth weight during first pregnancy.

Van Rijn and coworkers studied primiparous women who delivered between 1993 and 2002 at the University Medical Center Utrecht in The Netherlands who had a history of early onset preeclampsia resulting in delivery before 34 weeks of gestation.[8] Preeclampsia recurred in 25% (30/120) of women in their second pregnancy. Five percent delivered before 34 weeks of gestation and 17% between 34 and 37 weeks of gestation.

Sibai and colleagues[9] reported subsequent pregnancy outcomes in women with severe second trimester preeclampsia. Of these 125 women, 108 had 169 subsequent pregnancies. For the subsequent pregnancies, approximately one-third were normotensive and two-thirds were complicated by preeclampsia. Of the women with preeclampsia, approximately one-third developed a recurrence at <28 weeks, one-third at 28 to 36 weeks, and one-third at 37 to 40 weeks.

Preeclampsia Recurrence After HELLP Syndrome

Sibai and coworkers[10] described a retrospective analysis of 112 women with HELLP syndrome from 1977 to 1985. In this series, 38 women had 49 subsequent pregnancies.[10] One patient (2.6%) had recurrent HELLP syndrome in 2 subsequent pregnancies, both complicated by abruption and fetal death. These investigators extended their series to the years 1977 to 1992, with follow up on 341 patients, of which 152 had subsequent pregnancies.[11] Maternal complications included preeclampsia (19%), recurrent HELLP syndrome (3%), and placental abruption (2%). Perinatal complications included preterm birth (21%), intrauterine growth restriction (12%), and perinatal death (4%). Those with preexisting chronic hypertension had higher rates of preeclampsia (75%) but no significant increase in recurrent HELLP syndrome (5%). Perinatal complications such as preterm birth (80%), intrauterine growth restriction (45%), placental abruption (20%), and perinatal death (40%) were significantly higher among chronic hypertensives with previous HELLP syndrome. Interestingly, all of the above conditions, including preeclampsia, preterm birth, fetal growth restriction, placental abruption, and perinatal death, are considered to have overlapping etiologic mechanisms that relate to abnormal placentation. Thus, a pregnancy with preeclampsia in an initial pregnancy appears to be at risk for these other pregnancy complications and should be managed accordingly.

A retrospective study of 481 women with HELLP syndrome between the years 1980 and 1991 analyzed 161 of 195 subsequent pregnancies in 122 patients.[12] Of these 161 pregnancies, 43% had preeclampsia and 27% had HELLP syndrome. A previous delivery <32 weeks of gestation was a risk factor for recurrence of prematurity at a similar gestational age secondary to preeclampsia in 61% of cases.

Chames and coworkers reported the outcomes of subsequent pregnancies in women with a history of HELLP syndrome for which delivery occurred at <28 weeks of gestation.[13] Women were delivered in Memphis, TN (1984-1998) and Lexington, KY (1994-1998). Data were available in 69 patients; there were 76 subsequent pregnancies among 48 women, of which 62 progressed beyond 20 weeks of gestation. Preeclampsia developed in 55% (34), of which 7 were mild and 27 were severe. Recurrent HELLP occurred in 6%. There were no cases of eclampsia; however, significant perinatal complications were frequent. Preterm birth (<37 weeks of gestation) occurred in 53%. Newborns were growth restricted in 27%, and the overall perinatal mortality rate was 11%. Women with chronic hypertension had greater overall morbidity.

Preeclampsia Recurrence After Eclampsia

Eclampsia recurrence is to some extent dependent on adequacy of prenatal care and peripartum practices, including methods to control hypertensive crisis and prevention of eclamptic seizures vis-a-vis magnesium sulfate. Adelusi and Ojengbede[14] reported a prospective study of 64 eclamptics from Ibadan, Nigeria of whom 16% experienced recurrent eclampsia despite the benefit of antenatal care. Chesley's seminal account of eclampsia recurrence during the early 20th century reported a recurrence risk range of 0% to 21% from published series, with an approximately 5% risk for viable gestations.[15]

Sibai and coworkers studied 223 women whose pregnancies were complicated by eclampsia between the years 1977 and 1989, with an average follow up of 7.2 years.[16] Of the 366 subsequent pregnancies, 22% were complicated by preeclampsia and 1.9% by eclampsia. Within the nulliparous group, women who had eclampsia before 37 weeks of gestation in the index pregnancy had significantly higher incidences of preeclampsia and poor perinatal outcome in subsequent pregnancies, compared with those who had eclampsia at or beyond 37 weeks of gestation. Of the normotensive women, 10% had chronic hypertension on follow up. The highest incidence of chronic hypertension was in those with eclampsia at <30 weeks of gestation (18%) and the lowest incidence (5%) in those with eclampsia at >37 weeks of gestation.

Preeclampisa Recurrence After Multiple Gestations

Although multiple gestations are considered at risk for preeclampsia, it is not clear whether women developing this complication are clearly at risk for recurrence in the same degree as for singleton pregnancies. Only 1 study has addressed this issue. Trogstad and coworkers examined the Norway birth registry from 1967 to 1998, including 550,218 women.[17] For women with a previous singleton pregnancy complicated by preeclampsia, the recurrence rate was 14.1% compared with the recurrence rate for twins of 6.8%, which was much closer to the population risk. This suggests that different potential etiologies for preeclampsia present differ-

ent risks for recurrence. This is particularly important when designing a recurrence prevention strategy, since no single therapy would be expected to target all potential etiologies.

Clinical Features of Recurrent Preeclampsia

Hnat and coworkers[18] reported on 2934 nulliparous women with an initial episode of preeclampsia and 598 women with recurrent preeclampsia. Two of the more severe presentations of this disorder, eclampsia and HELLP syndrome, occurred in the nulliparous cases with an incidence of 0.34% and 0.21%, respectively. The same severe preeclampsia complications examined in the women with recurrent preeclampsia were approximately 5-fold higher: 1.67% for eclampsia and 1.00% for HELLP syndrome. In addition, recurrent preeclampsia was more commonly associated with other perinatal complications, such as preterm birth (67% versus 33%), abruptio placentae (8% versus 2%), and fetal death (7% versus 1%). Therefore, recurrent preeclampsia is clearly associated with more severe disease and with more severe associated morbidities.

Preeclampsia Pathogenesis Relevant to Recurrence

To understand the rationale and interpret some of the large randomized controlled trials aimed at preventing preeclampsia, it is important to understand proposed theories of the pathophysiology of this disorder. Most of the etiologies involve some form of physiologic change that promotes vascular endothelial damage, relative placental hypoxia, and oxidative stress injury.

1. Abnormal angiogenesis and resultant placental ischemia hypothesis: In this hypothesis poor second wave trophoblast invasion of the spiral arteries leads to placental ischemia which causes increased deportation of trophoblast into the maternal circulation which results in endothelial cell dysfunction.[19] Failed second wave invasion has been associated with many factors, including abnormal circulating levels of soluble fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and vascular endothelial growth factor (VEGF),[20] maternal infection with CMV,[21] prolactin abnormalities,[22] and deficiencies of trace metals.[23] Gene abnormalities linked with trophoblast invasiveness have also been proposed to influence preeclampsia risk.

2. Very low-density lipoprotein (VLDL) versus toxicity-preventing activity (TxPA) hypothesis: Arbogast and coworkers,[24] proposed that preeclampsia may result from an unusual accumulation of VLDL which leads to endothelial damage. This hypothesis was based on the observation that, in many women who subsequently develop preeclampsia, circulating free fatty acids (FFA) are increased 15 to 20 weeks before the onset of disease. These FFA adversely affect endothelial physiology leading to vasoconstriction. In some pregnant women (who are known to have low albumin concentrations), the burden of transporting extra FFA from adipose tissue to the liver as a response to the increased energy demands of pregnancy may reduce the concentration of TxPA to a point where the VLDLs cause endothelial injury.[24,25]

3. Hyperdynamic disease hypothesis: According to the hyperdynamic disease model,[26] early in pregnancy, preeclamptic patients have an elevated cardiac output with compensatory vasodilatation. As the disease progresses, there is a subsequent hemodynamic crossover to low cardiac output and high resistance circulation coinciding with the onset of the clinical syndrome. During the hyperdynamic phase, the dilated systemic terminal arterioles and renal afferent arterioles may expose capillary beds to systemic pressures and increased flow, eventually leading to endothelial cell injury characteristic of preeclampsia injury.[27]

4. Immune/immunogenetic maladaptation hypothesis: The interaction between decidual leukocytes and invading cytotrophoblast cells is essential for normal trophoblast invasion and development. Immune maladaptation may cause the shallow invasion of the spiral arteries by the endovascular cytotrophoblast cells, resulting in endothelial cell dysfunction mediated by an increased decidual release of cytokines, proteolytic enzymes, and free radical species.[28]

5. The genetic hypothesis: It has been hypothesized that the development of preeclampsia–eclampsia may be based on a single recessive gene or a dominant gene with incomplete penetrance, dependent on the fetal genotype. However, no specific genes have been identified and no defined inheritance pathway has been determined sufficient to clearly identify a specific gene pathway. There are data to support increased risk of preeclampsia in women who themselves were born of a preeclamptic pregnancy.[29] Women born of a normal pregnancy, but whose mother had preeclampsia with one her other pregnancies, also have an increased risk.[30] Esplin and coworkers[29] showed that not only do maternal genetics play a role, but men born of a preeclamptic pregnancy are more likely to father children from a preeclamptic pregnancy than those born of normal pregnancy. Skjaerven and colleagues suggest that the genes that determine maternal susceptibility to preeclampsia are different from the paternal genes that trigger preeclampsia through the fetus.[30]

6. Genetic-conflict hypothesis: In both flowering plants and mammalian pregnancies, there is genetic conflict due to competing interests of maternal and paternal genes regarding the volume of nutrients transferred from mother to fetus.[31] The more resources a fetus is able to take from its mother, the larger it will be at birth and the better its chances for survival and reproduction. However, the greater the nutritional demands of the pregnancy, the greater the cost to the mother's future reproductive potential. Paternal genes in the fetus and placenta may seek to maximize the transfer of nutrients from mother to baby (because the mother's future offspring may have a different father); maternal genes on the other hand tend to moderate the flow of resources in an effort to preserve her reproductive potential for future pregnancies. This inherent competition may contribute to genetic imprinting; that is, genes that behave differently in an organism depending on whether they were inherited from the mother or from the father. In mice, the paternal genes control the growth of the

Table 3 Proposed Evaluation Options for Women with a History Suggesting a High Rate of Preeclampsia Recurrence in Order to Target Interventions

History & physical examination
Chronic diseases
Family history
Other historical risk factors for recurrence
Review of placental pathology from previous affected pregnancy (eg, thrombi or infarcts, especially with fetal growth restriction, may benefit from low dose heparin)
Thrombophilia evaluation (inherited and acquired)
Antinuclear antibody if clinically suspicious for autoimmune disease
Early glucola if clinically appropriate
Baseline labs for later comparison
Complete blood count, platelets, serum creatinine, BUN, uric acid, liver enzymes, urinalysis, 24-hour urine for total protein content
Uterine artery Doppler screening to determine the intensity of ultrasound surveillance needed later in the pregnancy
Serial ultrasounds for evaluation of fetal growth
Antepartum fetal surveillance if indications present

placenta, whereas maternal genes are predominantly responsible for embryo formation. The placenta—as an agent of paternal genes—invades the maternal tissues to parasitize maternal blood supply and support fetal growth. The genetic conflict theory posits when for whatever reason placentation is abnormal and fetal growth is adversely impacted, the placenta somehow activates genes that enhance blood flow to the fetus at a cost to the mother. Preeclampsia may well represent such a situation, and recent data show that in this condition the placenta produces excess amounts of sFlt1 (soluble FMS like tyrosine kinase 1), leading to endothelial injury and vasoconstriction. Given the low resistance of the placental bed when maternal vasoconstriction occurs, a greater proportion of the maternal blood is shunted to the placental circulation. Data show that elevation in sFLT1 occurs well before the development of the clinical condition of preeclampsia.[20]

Recommended Evaluation and Management of Women at Risk for Recurrence

Because there are a significant number of risk factors and potential etiologic mechanisms leading to preeclampsia, an attempt should be made to identify those risk factors and pathways that offer opportunities for intervention. In this way, a rational pathway-specific strategy for prevention of preeclampsia recurrence can be developed. (Table 3).

Prevention of Recurrent Preeclampsia

Women with any of the following characteristics should be considered at particularly high risk for recurrent preeclampsia and stand to benefit the most from prevention strategies, even if there is only a modest effect on recurrence rates. These include preeclampsia that was complicated by high degree of severity, preterm birth, HELLP syndrome, eclampsia, fetal growth restriction, abruptio placenta, oligohydramnios, perinatal death, a strong family history, or a history of vascular lesions on placental histology. Women with any of these should be targeted for the most intensive etiologic evaluations and condition-specific therapy when warranted.

Only a few interventions have been sufficiently well-studied to demonstrate any consistent efficacy for preeclampsia recurrence prevention (Table 4). Antiplatelet therapy (primarily low-dose aspirin) has been studied most vigorously, and appears to provide a modest effect in preventing preeclampsia. Two published literature reviews have indicated that there is a 14-19% reduction in preeclampsia in high-risk women (especially those with previous preeclampsia) using low-dose aspirin, generally 81 mg/d.[32,33] It has been suggested that aspirin works through a variety of mechanisms, chiefly by increasing the prostacyclin to thromboxane ratio in the vascular endothelium and by reducing sensitivity to angiotensin II. However, other actions are also likely. Aspirin does not appear to be effective in preventing preeclampsia

Table 4 Reviews and Randomized Clinical Trials for Preeclampsia Recurrence Prevention

Agent	Study	Population	*N*	Odds Ratio (95% CI)
Aspirin	Coomarasamy[33]	High risk	12,416	0.86 (0.79-0.94)
	Duley[32]	High risk	33,439	0.81 (0.75-0.88)
Calcium	Hofmeyr[34]	Meta-analysis low risk	15,206	0.48 (0.33-0.69)
		Meta-analysis high risk	587	0.22 (0.12-0.42)
Magnesium	Spatling[35]	General low-risk	568	NS
	Sibai[36]	Normotensive primigravidas	374	NS
Fish oil	Makrides[37]	All risk	1,683	0.86 (0.59-1.27)
Vitamins C+E	Poston[41]	High risk	2,410	0.97 (0.80-1.17)
	Rumbold[42]	Nulliparous women	1,877	1.20 (0.82-1.75)
Heparin	Mello[46]	Angiotensin converting enzyme polymorphism in nonthrombophilic women with history of preeclampsia	80	0.26 (0.08-0.86)

Abbreviations: CI, confidence intervals; NS, not significant.

in low-risk women. Importantly, low-dose aspirin does not appear to have an appreciably increased risk of maternal, fetal, or neonatal complications. For at-risk pregnancies, it probably can be stopped at 36 weeks.

Calcium supplementation up to 2 g per day appears to decrease the incidence of preeclampsia significantly (12 trials with 15,206 women, RR = 0.48, 95% CI 0.33-0.69), with a greater effect in high-risk women that include those with previous preeclampsia (5 trials with 587 women, RR = 0.22, 95% CI 0.12-0.42) and those with low baseline calcium intake (7 trials with 10,154 women, RR = 0.36, 95% CI 0.18-0.70).[34] It may work via parathyroid hormone, by reducing intravascular calcium and lowering vascular contractility. The use of calcium to prevent preeclampsia in low-risk women is not supported by current literature.

Other potential therapies have been less well-studied, but available data are disappointing. Two small trials of magnesium sulfate showed no significant reduction in preeclampsia incidence.[35,36] Likewise, fish oil supplements, progesterone, and garlic have not been proven beneficial.[37-39] Because preeclampisa has been linked with an increase in oxidative stress, several therapies with antioxidants have been proposed. Most recently, vitamin C and vitamin E have been evaluated in large prospective randomized trials for preventing preeclampsia. An early review that examined initial trials suggested a potential benefit.[40] However, two recent, larger randomized trials by Poston and coworkers[39] and Rumbold and coworkers[41,42] have shown no such benefit and, in fact, indicated that there may actually be some potential harm.

Unfortunately, to date there have been no published randomized trials of therapy to prevent recurrence for women with previous preeclampsia who have a thrombophilia. Case series and anecdotal reports suggest a potential benefit of low-dose heparin (either unfractionated or low molecular weight).[43,44] This approach seems reasonable since placental vascular lesions are more common when there is a significant thrombophilia,[45] but prospective randomized trials are needed to support this as a standard of care.

Interestingly, heparin has been used to prevent preeclampsia recurrence in women with the angiotensin-converting enzyme insertion/deletion polymorphism and a history of preeclampsia. Mello and coworkers randomized 80 subjects with a history of preeclampsia who were without chronic disease or a demonstrable thrombophilia to either low molecular weight heparin prophylaxis or no treatment.[46] There were significant reductions in recurrence of preeclampsia (28% versus 7%), onset of preeclampsia ≤34 weeks (21% versus 2%), and fetal growth restriction (44% versus 10%). The authors also monitored uterine artery blood flow by Doppler and noted a significant improvement in uterine artery blood flow in the heparin treatment subjects. This suggests that heparin may have a therapeutic role for prevention of preeclampsia recurrence, but that role needs clarification.

At present there is no accepted consensus in the United States regarding the best approach in preventing preeclampsia in the general population or in high-risk women. The most recent American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin addressing preeclampsia, published in 2002, recommends no specific prophylactic regimen to prevent preeclampsia.[6] However, based on available data, it would seem reasonable, at the minimum, to offer calcium (2 g per day) and/or low-dose aspirin (81 mg per day) to high-risk women, given the perceived risk–benefit ratio. Heparin, especially low-molecular-weight preparations, may also be considered in the presence of previous preeclampsia with a significant thrombophilia, with placental vascular lesions, or after failure of calcium and low-dose aspirin therapy.

Future Direction

Clearly, more research is needed to identify and refine interventions to prevent the recurrence of preeclampsia. By focusing on this particularly high-risk population who have already had preeclampsia, it may be easier to successfully develop prevention strategies that can be applied to the lower risk women who lack obvious risk factors. Clinical areas needing significant clarification currently include thrombophilias in recurrent preeclampsia and identification of the women most likely to benefit from heparin preparations. Further insight into the pathophysiology of preeclampsia at the cellular and genomic level will likely create new opportunities for prevention. Recent reports looking at angiogenic proteins, such as circulating soluble fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), vascular endothelial growth factor (VEGF), and endoglin, have seemingly identified a pathogenic role for these factors in the development of preeclampsia.[20,41] It is not clear yet whether these can be useful for refining risk more precisely or if they might allow potential intervention points for therapy, but this area of research appears to have significant promise.[47]

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